UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,324	08/12/2005	Rasmus Dines Larsen	HOI-13202/16	5292

25006 7590 09/13/2007
GIFFORD, KRASS, SPRINKLE,ANDERSON & CITKOWSKI, P.C
PO BOX 7021
TROY, MI 48007-7021

EXAMINER	
CROW, ROBERT THOMAS	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
09/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/533,324	LARSEN ET AL.
	Examiner	Art Unit
	Robert T. Crow	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 87-129 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) 87-129 is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on 02 May 2005 is/are: a)☒ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☒ All b)☐ Some * c)☐ None of:
1.☒ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 8/05; 2/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendment

1. The Preliminary Amendment filed 12 August 2005 is acknowledged and has been entered. Claims 1-86 have been cancelled, and new claims 87-129 have been added.

Claims 87-129 are under prosecution.

Claim Objections

2. Claims 88 and 90 are objected to because of the following informalities: claims 88 and 90 each recite improper Markush groups. The limitations within a proper Markush group may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material <u>selected from</u> the group consisting of A, B, C <u>and</u> D" is a proper limitation, then "wherein R is A, B, C <u>or</u> D" shall also be considered proper (emphasis added by examiner). See MPEP § 2173.05(h). Claim 88 recited the particle is <u>selected from</u> ...<u>or</u> fragments or cluster thereof, <u>and</u> macromolecules <u>and</u> beads," while claim 90 recites "the particle <u>is selected</u> from...<u>and</u> macromolecules and beads" (emphasis added by examiner). Thus, neither claim properly recites either the conventional or the alternative manner.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 88-89, 91, 96-98, 102, 104-106, 111-114, 116, 118, 122, 123, and 125-127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 88-89 are indefinite in claim 88, which recites the limitation "or fragments or clusters thereof, and macromolecules and beads." The placement of the words "or" and "and" makes it

unclear which limitations are the alternative embodiments of the group, and if the "macromolecules and beads" are required structural limitations of the earlier listed embodiments or if they are alternatives to the earlier listed embodiments. It is suggested that the claim be amended to recite a proper Markush group.

B. Claims 91, 102, 104, 112, and 123 are each indefinite in the phrase "such as" because the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

C. Claims 96, 102, 104-105, 111, 116, and 118 are each indefinite for having recitations within parentheses because it is unclear if text within the parenthesis is explanatory material or additional limitations of the claim. It is suggested the claims be amended to recite only the specific limitations of the claim in alternative form.

D. Claims 97-98 are each indefinite in the recitation "the cells" because claim 87 done not recite any "cells." It is suggested the claims be amended to reflect proper antecedent basis.

E. Claims 104-106 and 116 are each indefinite in the term "e.g.," which means "for example," because "for example" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

F. Claim 106 is further indefinite in the recitation "phosphatidylserines targeted with Annexin V" in the lat two lines of the claim because it is unclear if the phosphatidyl serines or Annexin V is the target. It is suggested that the claim be amended to recite a proper Markush group that lists only the desired analytes.

G. Claim 113 is indefinite in the recitation "the labeling agent is selected from...antibodies labeled with reactive molecules" in lines 1-2 of the claim. It is unclear if the antibodies are in addition to the first targeting species or if the first targeting species with the label is the labeled antibody.

H. Claim 114 is indefinite in the recitation "the labeling agent is selected from...nucleotide probes labeled with reactive molecules" in lines 1-2 of the claim. It is unclear if the nucleotide probes are

in addition to the first targeting species or if the first targeting species with the label is the labeled nucleotide probe.

I. Claim 116 is indefinite in the recitation "further comprises" because the remainder of the claim done not contain either the word "and" or "or." Thus, it is unclear if the agents listed are alternative requirements of the claim or if the claim requires all of the listed agents. It is suggested that the claim be amended to recite a proper Markush group.

J. Claim 122 is indefinite in the recitation "without enlargement" at the end of the claim. Independent claim 87, upon which claim 122 depends, requires an enlargement. Thus, it is unclear how claim 122 can be dependent upon claim 87 because claim 87 requires a limitation that claim 122 specifically excludes.

K. Claims 123, 125, and 126-127 are indefinite in claims 123, 125, and 136, each of which recites broad limitations in the same claim as a narrow limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the instant claims, the following limitations are present in claims 123, 125, and 126:

I. Claim 123 recites the broad recitation "below 10," and the claim also recites "below 5," "below 4" and "below 2," each of which is a narrower statement of the range/limitation.

II. Claim 125 recites the broad recitation "or more," and the claim also recites "three" and "two," each of which is a narrower statement of the range/limitation.

III. Claim 126 recites the broad recitation " more than four," and the claim also recites "more than two" and "two," each of which is a narrower statement of the range/limitation.

L. Claim 123 is further indefinite in the recitation "such as 1" at the end of the claim. An enlargement ratio of 1 means that there is no enlargement. Independent claim 87, upon which claim 123 depends, requires an enlargement. Thus, it is unclear how the most preferred embodiment of claim 123 can be dependent upon claim 87 because claim 87 requires a limitation that the most preferred embodiment of claim 123 specifically excludes.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 87-89, 97-100, 107, 109, 112, 117-118, 120-123, and 129 are rejected under 35 U.S.C. 102(b) as being anticipated by Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995).

Regarding claim 87, Lea et al teach a method for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a

first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Regarding claim 88, Lea et al teach the method of claim 87, wherein the particle is a cell; namely, a blood cell (column 4, lines 25-45).

Regarding claim 89, Lea et al teach the method of claim 88, whereby the particle is a bead, to which analytes are bound; namely, in an alternate embodiment to that presented above, the magnetic particles bind to analytes other than cells (column 4, lines 65-68).

Regarding claim 97-98, Lea et al teach the method of claim 87, wherein the cells are blood cells (i.e., claim 99; column 4, lines 25-45); blood cells encompass mammalian cells (i.e., claim 97).

Regarding claim 99, Lea et al teach the method of claim 87, whereby the liquid material comprises at least two different species of particles; namely, the sample comprises biological cells and

cells other than those of interest (column 4, line 25-column 5, line 5). The cells are particles and the cells other than those of interest are at least one additional species of particles in addition to the biological cells, which are a first species of particles.

Regarding claim 100, Lea et al teach the method of claim 99, whereby only one of the species of particles has bound thereto or comprised therein the species of analyte; namely, the particles of interest are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). Because antibodies are highly specific, the antibodies bind only to one type of cell (i.e., particle) in the sample; namely, only to the cells having the analyte to which the antibodies bind.

Regarding claim 107, Lea et al teach the method of claim 87, wherein the at least one species of analyte is a medical marker of disease; namely, the counted cells are used to diagnose diseases (column 4, lines 25-40).

Regarding claim 109, Lea et al teach the method of claim 87, wherein the targeting species is an antibody to the analyte species; namely, the targeting species is the monoclonal antibody on the magnetic bead (column 4, line 25-column 5, line 5).

Regarding claim 112, Lea et al teach the method of claim 87, wherein the liquid material is a bodily fluid; namely, a blood sample (column 4, lines 25-40).

Regarding claims 117-118, Lea et al teach the method of claim 87, wherein the labeling agent is acridine orange; namely, the beads are also attached via direct coupling to a fluorescent labeling agent, which is a dye, via a sandwich complex (column 4, line 25-column 5, line 5), wherein the fluorescent dye is acridine orange (column 5, lines 34-36).

Regarding claims 120-121, Lea et al teach the method of claim 87, wherein the image is recorded using an array of detection devices; namely, the recording is made with a CCD array (column 5, lines 9-40).

Regarding claims 122-123, Lea et al teach the method of claim 87. It is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Thus, the teaching of Lea et al that the flat image **may** be magnified encompasses the alternate embodiment wherein the image is **not** magnified (i.e., claim 122). See MPEP § 2123 [R-5]. A non-magnified image would have an enlargement ratio of 1 (i.e., claim 123).

Regarding claim 129, Lea et al teach the method of claim 87, whereby the recording of the image comprises exposing a first surface of the sample directly with excitation light from a first light means having a first light source; namely, Lea et al teach Figure 1, which shows excitation light from ultraviolet light source 2, which is a light means having a light source, entering cell 1 through a side wall and thereby directly striking a first surface of the sample, which is the collection of particles within cell 1. Lea et al further teach the particles then fluoresce (Abstract), and the fluorescence signal travels from the cell through lens 3, which is a focusing means (column 5, lines 5-55). Light from lens 3 then passes to CCD array 5, which is a first detection means comprising at leas a first detector (column 5, lines 5-55 and Figure 1).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 87, 90, 95-96, 103, 113-114, and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Fan et al (U.S. Patent Application Publication No. US 2002/0001801 A1, published 3 January 2002).

Regarding claims 90, 95-96, and 103, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column

5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

While Lea et al also teach, in an alternate embodiment to that presented above, the magnetic particles bind to analytes other than cells (column 4, lines 65-68), Lea et al do not teach the analyte is a nucleic acid (i.e., claim 90) or a chromosomal DNA sequence (i.e., claim 103), having between 500 and 50,000 analyte detectable positions (i.e., claim 96), which is less than $5x10^5$ analyte detectable positions (i.e., claim 95).

However, Fan et al teach the detection of nucleic acid analytes comprising the use of microparticles. In a single exemplary embodiment, Fan et al teach analyte nucleic acids in the form of nucleic acids immobilized onto microspheres (Abstract), which are particles. The nucleic acids are genomic DNA from a human sample (i.e., claim 90; paragraph 0026), which is a chromosomal DNA

sequence (i.e., claim 103). The nucleic acid is any length (paragraph 0032) including less than 1000 bases (paragraph 0081), which is between 500 and 50,000 analyte detectable positions (i.e., claim 96), which is less than $5x10^5$ analyte detectable positions (i.e., claim 95). Fan et al also teach use of nucleic acids as target analytes has the added advantage of allowing analysis of single nucleotide polymorphisms, which are indicative of disease disposition (paragraph 0006).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the nucleic acid analytes on microparticles as taught by Fan et al with a reasonable expectation of success. The modification would have resulted in nucleic acid analytes (i.e., claim 90) using chromosomal DNA in the form of genomic DNA from a human sample (i.e., claim 103) having a length of between 500 and 50,000 analyte detectable positions (i.e., claim 96), which is less than $5x10^5$ analyte detectable positions (i.e., claim 95). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing analysis of single nucleotide polymorphisms, which are indicative of disease disposition, as explicitly taught by Fan et al (paragraph 0006).

Regarding claims 113-114, the method of claim 87 is discussed above. Lea et al do not teach the labeling agent is a fluorescently labeled antibody (i.e., claim 113) or a fluorescently labeled oligonucleotide probe (i.e., claim 114).

However, Fan et al labeling agents in the form of labeled decoder binding ligands (i.e., DBLs; paragraph 0069). The DBLs are either antibodies (i.e., claim 113) or oligonucleotides in the form of nucleic acids (i.e., claim 114; paragraph 0074), and the labels are fluorescent (paragraph 0075). Fan et al also teach the fluorescently labeled DBLs have the added advantage of allowing decoding of the analyte particles (i.e., IBLs; paragraph 0071), which aids in the identification of the species of particle that has a target species bound thereto.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the labeled DBLs as labeling reagents as taught by Fan et al with a reasonable expectation of success. The modification would have resulted in a labeling agent is either a fluorescently labeled antibody (i.e., claim 113) or a fluorescently labeled oligonucleotide probe (i.e., claim 114). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing decoding of the analyte particles which aids in the identification of the species of particle that has a target species bound thereto, as explicitly taught by Fan et al (paragraph 0071).

Regarding claim 116, the method of claim 87 is discussed above. Lea et al do not teach the reagent material further comprises fluorescence quenching agents.

However, Fan et al teach a reagent material in the form of a molecular beacon, which comprises a first targeting species in the form of a hairpin probe and a labeling agent in the form of a fluorescent label. The molecular beacon further comprises a fluorescence quencher, and has the added advantage of increased signal strength upon binding to the target (paragraph 0152).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the reagent materials comprising fluorescence quenchers as taught by Fan et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of increased signal strength upon binding to the target as explicitly taught by Fan et al (paragraph 0152).

10. Claims 87-88, 91, 102 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Baer et al (U.S. Patent No. 5,547,849, issued 20 August 1996).

Regarding claims 91, 102 and 107, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3,

lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al also teach the method of claim 88, wherein the particle is a cell; namely, a blood cell (column 4, lines 25-45).

Lea et al do not teach the analyte is a cell receptor bound to a cell membrane (i.e., claim 91). CD4 is a cell receptor bound to a cell membrane (i.e., claim 102), which is a marker of the disease AIDS (i.e., claim 107).

However, Baer et al teach the detection of leukocytes having CD4 on their surface, which has the added advantage of determining the progression of AIDS (column 8, lines 15-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the detection of the cell receptor CD4 (i.e., claim 102), which is a cell receptor bound to a cell membrane (i.e., claim 91) and is a marker of a disease (i.e., claim 107), as taught by Baer et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of determining the progression of AIDS as explicitly taught by Baer et al (column 8, lines 15-50).

11. Claims 87-88, 92-93, 103, and 110-111 rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Singer et al (U.S. Patent No. 5,728,527, issued 17 March 1998).

Regarding claims 92-93, 103, and 110-111, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less

that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al also teach the method of claim 88, wherein the particle is a cell; namely, a blood cell (column 4, lines 25-45).

Lea et al do not teach the analyte is a chromosomal DNA sequence (i.e., claim 103) comprised in a cell (i.e., claim 92). Chromosomal DNA sequences within a cell are inside the nucleus, which is an organelle (i.e., claim 93). Probes that bind chromosomal DNA sequences within a cell are in situ

hybridization probes (i.e., claim 111), and are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110).

However, Singer et al teach in situ hybridization probes (i.e., claim 111), which bind to specific sequences on chromosomal DNA (i.e., claim 103; column 2, lines 19-45) and are nucleotide probes complementary to a sequence of an analyte species (i.e., claim 110). Chromosomal DNA sequences are inside the nucleus, which is an organelle (i.e., claim 93), and are thus comprised inside a cell (i.e., claim 92). Singer et al further teach in situ hybridization probes have the added advantage of determining the expression level of genes during specific developmental stages (i.e., larval and embryonic stages; column 2, lines 19-45).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the in situ hybridization probes as taught by Singer et al with a reasonable expectation of success. The modification would result in a method using in situ hybridization probes (i.e., claim 111), which are a targeting species that is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110), to bind to specific sequences on chromosomal DNA (i.e., claim 103), which are inside an organelle in the form of the nucleus of the cell (i.e., claim 93), and are thus comprised inside a cell (i.e., claim 92). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the expression level of genes during specific developmental stages as explicitly taught by Singer et al (column 2, lines 19-45).

12. Claims 87-88, 92, and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Connors et al (U.S. Patent No. 5,726,009, issued 10 March 1998).

Regarding claims 92 and 94, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al also teach the method of claim 88, wherein the particle is a cell; namely, a blood cell (column 4, lines 25-45).

Lea et al do not teach the analyte is on the surface of an organelle (i.e., claim 94); organelles are inside the cell (i.e., claim 92).

However, Connors et al teach the detection of an analyte on the surface of an organelle; namely, a targeting species/labeling agent in the form of a dye binds to the nuclear membrane. The nuclear membrane is the surface of the nucleus, which is an organelle and is comprised in a cell (i.e., claim 92; column). Thus, the analyte is the nuclear membrane, which is located on the surface of the organelle (i.e., claim 94). Connors et al also teach the detection of the nuclear membrane (i.e., as an analyte) has the added advantage of identifying dead cells, thereby allowing determination of the number of viable cells in a population (column 6, lines 9-30).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the detection of analytes on the surface of an organelle as taught by Connors et al with a reasonable expectation of success. The modification would result in a method that detects the nuclear membrane, which is on the surface of an organelle (i.e., claim 94) which is comprised inside a cell (i.e., claim 92). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing determination of the number of viable cells in a population by identifying dead cells as explicitly taught by Connors et al (column 6, lines 9-30).

13. Claims 87, 101, 108, and 110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Singer et al (U.S. Patent No. 5,573,909, issued 12 November 1996)..

Regarding claims 101, 108, and 110, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al also teach the simultaneous counting (i.e., detection) of more than one population of cells (i.e., analytes) simultaneously using different colors (column 3, lines 38-50). Lea et al do not explicitly teach the two distinct populations are bound by two distinct targeting species using two distinct colored labels; i.e., multiplex detection (i.e., claims 101 and 108). Lea et al also do not teach the targeting species is a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110).

However, Singer et al teach the targeting of at least two distinct species of analyte; namely, more than one target material is targeted using reagent material comprising multiple microparticles each having a different target complement, which is a distinct targeting species (i.e., claim 108), and having a difference fluorescent labeling agent (i.e., claim 101; column 16, lines 54-65). The target complements are nucleotide probes complementary to a sequence of an analyte species (i.e., claim 110; column 15, lines 50-67), which has the added advantage of allowing simultaneous analysis of different genes (column 18, lines 1-22).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the multiplex detection as taught by Singer et al with a reasonable expectation of success. The modification would result in two distinct populations bound by two distinct targeting species using two distinct colored labels (i.e., claims 101 and 108) using a nucleotide probe complementary to a sequence of an analyte species (i.e., claim 110). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing simultaneous analysis of different genes as explicitly taught by Singer et al (column 18, lines 1-22).

14. Claims 87, 104, and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Brechot et al (U.S. Patent No. 5,849,508, issued 15 December 1998).

Regarding claims 104 and 107, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al do not teach detection of a cell cycle related protein (i.e., claim 104); namely, cyclin A, which is a medical marker of a disease (i.e., claim 107).

However, Brechot et al teach the detection of a cell cycle related protein, in the form of cyclin A (i.e., claim 104), which is a medical marker of the disease hepatocellular carcinoma (i.e., claim 107; Abstract). Brechot et al further teach detection of cyclin A has the added advantage of allowing detection and treatment of tumorigenesis at an early stage (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the detection of a cell cycle related protein as taught by Brechot et al with a reasonable expectation of success. The modification would result in detection of a cell cycle related protein (i.e., claim 104) using a medical marker of a disease (i.e., claim 107). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing detection and treatment of tumorigenesis at an early stage as explicitly taught by Brechot et al (Abstract).

15. Claims 87, 105, and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Draetta et al (U.S. Patent No 5,691,147, issued 25 November 1997).

Regarding claims 105 and 107, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that 1×10^6 analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic

beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al do not teach detection of a cell cycle related protein receptor (i.e., claim 105); namely, CDK4, which is a medical marker of a disease (i.e., claim 107).

However, Draetta et al teach the detection of the level of CDK4 in a binding assay (column 25, line 65-column 26, line 35), wherein CDK4 is strongly implicated in the control of cell proliferation during the G1 phase (column 1, lines 2-42). Determination of cell proliferation aids in the determination of the risk of certain disorders in humans (i.e., claim 107; column 3, lines 50-55).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on

microparticles as taught by Lea et al with the detection of a cell cycle related protein receptor as taught by Draetta et al with a reasonable expectation of success. The modification would result in detection of a cell cycle related protein receptor (i.e., claim 105) using a medical marker of a disease (i.e., claim 107). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of aiding in the determination of the risk of certain disorders in humans by determination of the amount of cell proliferation as explicitly taught by Draetta et al (column 1, lines 2-42 and column 3, lines 50-55).

16. Claims 87, 106, and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Bitler et al (U.S. Patent No. 6,379,882 B1, issued 30 April 2002).

Regarding claims 106-107, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is

made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al do not teach detection of a marker of apoptosis (i.e., claim 106); namely, Annexin V, which is a medical marker of a disease (i.e., claim 107).

However, Bitler et al teach detection of phosphatidylserines targeted with Annexin V, which has the added advantage of allowing quantitation of apoptotic cells (column 12, lines 31-54).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the detection of phosphatidylserines targeted with Annexin V as taught by Bitler et al with a reasonable expectation of success. The modification would result in detection of a marker of apoptosis (i.e., claim 104) using a medical marker of a disease (i.e., claim 107). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing quantitation of apoptotic cells as explicitly taught by Bitler et al (column 12, lines 31-54).

17. Claims 87, 115, and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995).

Regarding claim 115, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that 1×10^6 analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al also teach the addition of lysing agents (column 4, lines 55-65). While Lea et al do not teach the lysing agents are added with the targeting species/labeling agent as part of the reagent material, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C.

Regarding claim 128, the method of claim 87 is discussed above.

Lea et al do not explicitly teach a distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles as an embodiment of the invention of Lea et al.

However, Lea et al do teach a method wherein a distinction between at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles; namely, the spectral properties of light scattering and fluorescence of the particles are measured, which has the added advantage of providing information on the surface structure of the particles (i.e., cells) as well as provide information about the fluorescent labels themselves (column 1, lines 30-41).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the use at least two spectral properties of a labeling agent is used to obtain at least one quality or quantity parameter of the particles as taught by Lea et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of providing information on the surface structure of the particles as well as provide information about the fluorescent labels themselves as explicitly taught by Lea et al (column 1, lines 30-41).

18. Claims 87 and 119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Mathies et al (U.S. Patent No. 6,100,535, issued 8 August 2000).

Regarding claim 119, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3,

lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al do not teach the recording of the image comprises the use of a confocal scanner.

However, Mathies et al teach the use of confocal scanners, which have the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals (column 5, lines 10-16).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the use of a confocal scanner to record the image as taught by Mathies et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of permitting high sample rates with simultaneous detection of multiple colors of fluorescent signals as explicitly taught by Mathies et al (column 5, lines 10-16).

19. Claims 87 and 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Yoshikawa et al (U.S. Patent No. 5,115,304, issued 19 May 1992).

Regarding claim 124, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5).

The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al do not teach the image is recorded in a single exposure.

However, Yoshikawa et al teach recorded images created from a single exposure have the added advantage of not requiring a lot of memory space to record the image (column 1, lines 40-45).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the recording of the image in a single exposure as taught by Yoshikawa et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method

having the added advantage of not requiring a lot of memory space to record the image as explicitly taught by Yoshikawa et al (column 1, lines 40-45).

20. Claims 87 and 125-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lea et al (U.S. Patent No. 5,428,541, issued 27 June 1995) in view of Hart (U.S. Patent No. 5,850,485, issued 15 December 1998).

Regarding claim 125, Lea et al teach the method of claim 87 for assessing at least one quality or quantity parameter of a particle in a liquid material. In a single exemplary embodiment, Lea et al teach a liquid material (i.e., fluid) comprising particles (column 2, lines 19-35). The particles are blood cells (column 4, lines 25-45), and thus have bound thereto or comprised therein less that $1x10^6$ analyte detectable positions because page 9 of the instant specification recited blood cells as a preferred form of particle. The particles are bound to reagents in the form of superparamagnetic beads (i.e., particles), which selectively and directly bind an analyte position of said species of analyte because the magnetic beads are attached to selected cells by specific monoclonal antibodies (column 4, line 25-column 5, line 5). The antibodies are a first targeting species. The beads are also attached via direct coupling to a fluorescent labeling agent via a sandwich complex (column 4, line 25-column 5, line 5). Fluorescent labels absorb and emit electromagnetic radiation in the form of light to generate a detectable electromagnetic signal. The fluid containing the particles is then passed through an optical cell (column 2, lines 19-67), which is a sample compartment having a wall part defining an exposing area wherein electromagnetic signals from the sample pass through the wall to the exterior; namely, Figure 1 shows the cell , which is made of optical quality material, allows light to pass through (column 5, lines 9-40). The light that passes through the wall part is then exposed onto an array of detection elements in the form of a CCD array (column 5, lines 9-40). The representation of the light signals is subjected to a linear enlargement so that the ratio of the enlargement is smaller that 20:1; namely, the image is of the particles is magnified in the range of 2 to 15 (column 2, lines 50-60). The representation is detected as intensities by individual active

detection elements; namely, each CCD in the array provides a picture of the particles (column 2, line 50-column 3, line 37). The intensities are processed in order to separate the particle signals from the background; namely, contrast between the particle images an the background is maximized (column 3, lines 50-67), and at least one quality or quantity parameter is obtained from the processing; namely, the cells are counted (column 3, lines 65-68).

Lea et al do not teach the image is recorded in multiple exposures.

However, Hart teaches multiple exposed images, which have the added advantage of allowing the measurement of very high flow rates (column 3, lines 60-63).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising detection of analytes on microparticles as taught by Lea et al with the recording of the image in multiple exposures as taught by Hart with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having the added advantage of allowing the measurement of very high flow rates as explicitly taught by Hart (column 3, lines 60-63).

Regarding claim 126, the method of claim 125 is discussed above. Lea et al also teach the assessment of the number of particles is obtained on the basis of more than four images; namely, the images are sampled as ten freeze frame pictures, which are used to assess the number of particles by identifying the number of illuminated objects (i.e., particles; column 5, lines 54-67).

Regarding claim 127, the method of claim 125 is discussed above. Lea et al further teach information about the changes in the image in course of time is used in the assessment of the number of particles; namely, the freeze frame images provide real time information about the number of illuminated objects (i.e., particles; column 5, lines 54-67).

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jehanne Sitton
JEHANNE SITTON
PRIMARY EXAMINER
9/4/07

Robert T. Crow
Examiner
Art Unit 1634